UNITED STATES OF AMERICA
BEFORE THE FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

In the Matter of: Enrofloxacin for Poultry: Withdrawal of Approval of Bayer Corporation's New Animal Drug Application (NADA) 140-828 (Baytril)	FDA DOCKET: 00N-1571 DATE: July 26, 2002

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The Center for Veterinary Medicine's Response to Bayer's June 24, 2002, Interrogatories

The Center for Veterinary Medicine ("the Center" or "CVM") submits the following Responses to Bayer's June 24, 2002 Interrogatories to CVM. As agreed upon between counsel for CVM and counsel for Bayer, CVM has answered the "contention" or other interrogatories but has not specifically identified which documents in Docket No. 00N-1571 support the response to each Interrogatory. Nothing in 21 C.F.R. Part 12 requires the Center to submit a cross-index to documents supporting responses to Interrogatories.

Responses to Interrogatories

1. Identify all facts and data on which CVM relies for its position that fluoroquinolone use in chickens (and separately for turkeys) acts as a selection pressure resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* spp. in chickens (and separately for turkeys)

Answer: CVM objects to this and all subsequent interrogatories that request CVM to "identify all facts and data" as overly burdensome and not anticipated or required by the governing regulations (21 C.F.R. Part 12). Pursuant to agreement between counsel

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from CVM and Bayer, CVM will provide responses to "contention" and other interrogatories, but will not parse out or cross-index supporting documentation already provided in Docket No. 00N-1571. Notwithstanding this objection, CVM responds as follows:

Chickens:
As stated in CVM's Notice of Opportunity for Hearing, "Scientific evidence demonstrates that the use of antimicrobials in food-producing animals can select for resistant bacteria of human health concern. Repeated dosing of food-producing animals can also contribute to the selection of resistant bacteria . . . ." When an antimicrobial drug is administered to an animal, it promotes the emergence of resistance in bacteria that may not be pathogenic to the animal, but are pathogenic to humans. For example, *Salmonella* and *Campylobacter* are ubiquitous and can exist in the intestinal flora of various food-producing animals without causing disease in the animals. Selective pressure exerted by fluoroquinolone use is the driving force for the development and spread of fluoroquinolone resistance in large numbers of animals through water or feed, and facilitates the spread of resistant pathogens. Despite restrictions placed by FDA on the use of the approved poultry (chicken and turkey) fluoroquinolone products, fluoroquinolone resistance among *Campylobacter* organisms isolated from chickens, turkeys and humans developed and increased after the 1995 and 1996 approvals.

Additionally, due to the nature of poultry production, the most efficient way to administer drugs is through the water or feed supply. Baytril Concentrate Antimicrobial Solution is a product administered in the water. When disease is detected in a poultry house, the product is administered in the water to all the birds in the house, thereby exposing all of the birds in that house, rather than just the birds displaying clinical signs of the disease. The practice of treating all the birds in an entire house increases selection pressure. Moreover, the dose administered to each bird is variable when the antimicrobial is administered in the water. This practice may result in ineffective dosing in some birds and increase the probability of selecting for resistant zoonotic bacteria in some healthy and diseased birds.

Data and information to support these statements may be found in Docket No. 00N-1571.

Turkeys:
See the answer to chickens.

2. Identify specifically when CVM first understood that fluoroquinolone use in chickens (and separately for turkeys) could act as a selection pressure resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* species in chickens (and separately for turkeys).

Answer:

Chickens:
To the best of CVM's information and belief, the Center understood that fluoroquinolone use in chickens could act as a selection pressure resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* species in chickens in late 1993 or early 1994. This timeframe coincided with preparations for the Joint Veterinary Medicine and Anti-infective Drugs Advisory Committee meeting that took place in May 1994. Although individual CVM employees or other persons working on CVM's behalf in this matter may have known earlier that fluoroquinolone use in chickens could act as a selection pressure resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* species in chickens, it was accepted by CVM management in late 1993 or early 1994.

Turkeys:
See the answer to chickens.

3. If CVM's answer to Interrogatory No. 2 is earlier than October 4, 1996, please identify in what way, if any, CVM's current understanding that fluoroquinolone use in chickens (and separately for turkeys) can act as a selection pressure resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* species in chickens (and separately for turkeys) differs from CVM's understanding of the issue prior to October 4, 1996.

Answer:

Chickens:
CVM's current understanding that fluoroquinolone use in poultry can act as a selection pressure resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* in poultry differs from the Center's understanding of the issue prior to October 4, 1996, in the degree to which the selection pressure occurs and the inadequacy of approved labeling conditions to prevent such fluoroquinolone-induced resistance.

In late 1993 or early 1994 CVM became aware of certain foreign studies demonstrating that fluoroquinolone use in poultry can act as a selection pressure and result in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter*. These studies may be found in Docket No. 00N-1571.

Due to the nature of the controversy surrounding the use of fluoroquinolones in food-producing animals, FDA held a joint veterinary medicine and anti-infective drugs advisory committee in May 1994 to address the specific issue of approval of fluoroquinolones for use in poultry. The committee advised the agency that if the products were approved, several restrictions should be placed on the use of the drugs in order to minimize the public health risks related to the development of resistant bacteria in animals. These restrictions included approval of fluoroquinolones for therapeutic use by veterinary prescription only, prohibition of extra-label use, and monitoring of resistance in both humans and animals.

The fluoroquinolones were approved for therapeutic use in poultry by veterinary prescription. After approval, one of the first actions the Center took to minimize the potential public health risks was to prohibit all extra-label uses of fluoroquinolones in food-producing animals. This order, which became effective in August 1997 (21 CFR 530.4), also provided the Center with the authority necessary to enforce the prohibition.

As a result of the advisory committee recommendations, FDA established the National Antimicrobial Resistance Monitoring System (NARMS) in 1996 to prospectively monitor changes in antimicrobial susceptibilities of selected enteric bacteria.

At the time the drug was approved, CVM was aware of certain limited foreign studies. Since the time enrofloxacin has been approved, there has been a great deal of additional research on the issue of fluoroquinolone use in poultry acting as a selection pressure and resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* in poultry. These studies can be found in Docket No. 00N-1571 and support CVM's current understanding that fluoroquinolone use in poultry results in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* species in poultry.

Turkeys:
See the answer to chickens.

4. Does CVM contend that fluoroquinolone use in chickens (and separately for turkeys) is the only cause of the development of fluoroquinolone-resistant *Campylobacter* species in chickens (and separately for turkeys)?

Answer:

Chickens:
No.

Turkeys:
No.

5. If CVM's answer to Interrogatory No. 4, above, is anything other than an unqualified "yes," please identify in order of relative significance all other causes of the development of fluoroquinolone-resistant *Campylobacter* species in chickens (and separately for turkeys) known to CVM.

Answer:

Chickens:

Fluoroquinolone use in chickens is the driving selection force for emerging fluoroquinolone-resistant *Campylobacter* species in chickens and turkeys. This does not mean that every chicken or turkey carrying flurorquinolones-resistant *Campylobacter* had to have been treated with a fluoroquinolone. Multiple examples in the scientific literature indicate mutations in the DNA gyrase of *Campylobacter* are responsible for high level fluoroquinolone resistance which are selected via fluoroquinolone exposure.

Turkeys:
See the answer to chickens.

6. Identify all facts and data on which CVM relies for its position that fluoroquinolone-resistant *Campylobacter* spp. in chickens (and separately for turkeys) are transferred to humans and contribute to fluoroquinolone-resistant *Campylobacter* infections

Answer: Numerous studies, including those noted in the Notice of Opportunity for Hearing, have indicated a strong association between eating chickens (and turkeys) and acquiring both human fluoroquinolone-susceptible and fluoroquinolone-resistant *Campylobacter* infections. These studies and other supportive information can be found in Docket No. 00N-1571.

7. Identify when CVM first understood the potential for fluoroquinolone-resistant *Campylobacter* to be transferred from chickens (and separately for turkeys) to humans and contribute to fluoroquinolone-resistant *Campylobacter* infections in humans.

Answer:

Chickens:
To our best information and belief, CVM first understood that the potential existed for fluoroquinolone-resistant *Campylobacter* to be transferred from poultry to humans (thus contributing to fluoroquinolone-resistant *Campylobacter* infections in humans) some time prior to the May 11, 1994 joint meeting of the Veterinary Medicine Advisory Committee and the Anti-infective Drugs Advisory Committee (Gaithersburg, Maryland). Although individual CVM employees or other persons working on CVM's behalf in this matter may have known earlier, the potential for fluoroquinolone-resistant *Campylobacter* to be transferred from poultry to humans (and contribute to subsequent fluoroquinolone-resistant *Campylobacter* infections in humans) was accepted by CVM management in late 1993 or early 1994.

Turkeys:
See the answer to chickens.

8. If CVM's answer to Interrogatory No. 7 is earlier than October 4, 1996, identify in what way, if any, CVM's current understanding of the potential for

fluoroquinolone-resistant *Campylobacter* to be transferred from chickens (and separately for turkeys) to humans and contribute to fluoroquinolone-resistant *Campylobacter* infections in humans differs from CVM's understanding of the potential prior to October 4, 1996.

Answer: CVM's current understanding of the potential for fluoroquinolone-resistant *Campylobacter* to be transferred from chickens to humans and contribute to fluoroquinolone-resistant *Campylobacter* infections in humans differs from our understanding prior to October 4, 1996. Implementation of strategies intended to mitigate the development of fluoroquinolone resistance in *Campylobacter* (such as approval restrictions, surveillance, and educational activities) proved ineffective. At the time of approval of enrofloxacin for poultry, CVM was also not aware of the impact that use of fluoroquinolones in poultry would have on human health. That question was answered with the CVM *Campylobacter* risk assessment.

The *Campylobacter* risk assessment provided CVM with evidence of the magnitude of the impact of fluoroquinolone use in chickens by establishing that this use of fluoroquinolones has a negative impact on human health.

While CVM recognizes that turkeys and chickens are separate species, the limited data that is available on fluoroquinolone susceptible and resistant *Campylobacter* isolated from turkeys and turkey products indicate epidemiological similarities between the two species with regard to transfer of these organisms to humans.

9. Does CVM contend that transfer of fluoroquinolone-resistant *Campylobacter* from chickens (and separately for turkeys) to humans is the only cause of fluoroquinolone-resistant *Campylobacter* infections in humans?

Answer: No.

10. If CVM's answer to Interrogatory No. 9, above, is anything other than an unqualified yes, please identify in order of relative contribution all other causes of the development of fluoroquinolone-resistant *Campylobacter* spp. in humans known to CVM.

Answer: Human use of fluoroquinolones can lead to fluoroquinolone-resistant *Campylobacter*. However, one study suggests that fluoroquinolone use in humans could account for no more than 15% of all fluoroquinolone-resistant cases acquired domestically. This and other supporting studies may be found in Docket No. 00N-1571.

11. Does CVM contend that transfer of fluoroquinolone-resistant *Campylobacter* from chickens (and separately for turkeys) to humans is a statistically detectable cause of fluoroquinolone-resistant *Campylobacter* infections in humans?

Answer:

Chickens:
Yes. These studies may be found in Docket No. 00N-1571.

Turkeys:
See the answer to chickens.

12. If CVM's answer to Interrogatory No. 11 is anything other than an unqualified "no," identify all statistical tests and data analyses that indicate a causal relation between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans.

Answer: CVM does not have data on fluoroquinolone use in chickens. CVM relied on a test of trends in increasing rates of fluoroquinolone resistance in humans (in Minnesota) in the years following the approval of fluoroquinolones for use in chickens. [Smith (G-588) and (G-589) in Docket No. 00N-1571]. The causal relationship between fluoroquinolone use in poultry and increased cases of fluoroquinolone resistance is inferred because of this temporal relationship and other scientific information cited in Numbers 1-10.

13. Has CVM performed any formal statistical tests of the causal hypothesis that fluoroquinonlone use in chickens causes increases in fluoroquinolone-resistant *Campylobacter* infections in humans? If yes, please specify the causal tests, the significance levels used, and the results.

Answer: No. In order to be able to directly test the causal hypothesis that fluoroquinolone use in chickens causes increases in human cases of fluoroquinolone resistant campylobacteriosis, one needs to have knowledge of both use levels of fluoroquinolones in chickens and the concurrent associated levels of the human cases of campylobacteriosis. CVM does not have information on the quantity of fluoroquinolones being used in chickens.

14. Has CVM performed any formal statistical tests of the causal hypothesis that fluoroquinonlone use in chickens reduces fluoroquinolone-resistant *Campylobacter* infections in humans? If yes, please specify the causal tests, the significance levels used, and the results.

Answer: No. Please see the response to No. 13 above.

15. Has CVM performed any Granger-Sims test for causality in any sets of time series that involve fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans? If yes, please specify the significance levels used and the results.

Answer: No. As the time series for annual fluoroquinolone use in chickens is nonexistent, the Granger-Sims test for causality involving fluoroquinolone use in chickens, per se, cannot be performed. Please see the response to No. 13 above.

16. Has CVM performed any conditional independence tests for possible causality in any sets of data that involve fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans? If yes, please specify the significance levels used and the results.

Answer: No. Please see the response to No. 13 above.

17. Has CVM developed any causal graph models or path analysis models from data that involve fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans? If yes, please specify the results, especially any finding from the data of a possible causal relation between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans.

Answer: Because "causal graph model or path analysis models" were not defined by Bayer in its interrogatory, CVM cannot respond with a "yes" or "no" answer. CVM's risk assessment is based on a fault-tree approach that was taken in light of the epidemiological data available on fluoroquinolone-resistant *Campylobacter* infections in humans and proportions of chicken carcasses with fluoroquinolone-resistant *Campylobacter*. A fault-tree creates a path back from an adverse outcome to its possible causes. As mentioned in the response to No. 13 above, CVM had scientific input that without selection pressure from fluoroquinolones, resistance levels in *Campylobacter* are negligible. At the time the risk assessment was conducted in the U.S., there were two main exposures of *Campylobacter* to fluoroquinolones: use in poultry and use in humans. From studies in the literature CVM knew that humans were exposed in the U.S. to *Campylobacter* from consumption of or contact with chicken or food that had been in contact with chicken and that some of the *Campylobacter* on chicken were fluoroquinolone-resistant. CVM also knew that some humans were similarly exposed to fluoroquinolone-resistant *Campylobacter* through foreign travel. CVM also knew that some fluoroquinolone-resistant *Campylobacter* infections detected in humans were the result of people having taken a fluoroquinolone prior to submitting their stool samples for culture. Information on what proportion of resistant cases were associated with foreign travel and what proportion were associated with prior fluoroquinolone use was available. Starting the fault-tree with the estimated number of human cases with fluoroquinolone-resistant *Campylobacter* infections attributable to chicken and given the proportions of resistant cases associated with two sources out of three possible sources, it is a simple

matter of exclusion to obtain the number of cases associated with the third source. Data on the two identified sources came from a recent (1998-99) case-control study conducted by CDC. This and other supporting studies may be found in the risk assessment document in Docket No. 00N-1571.

18. Has CVM performed any formal statistical tests for omitted explanatory variables and/or confounders in analyzing possible statistical associations between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans? If yes, please specify the tests used and the results obtained.

Answer: No, CVM used an estimation process rather than statistical testing. As indicated in the response to No. 13 above, CVM did not have data on fluoroquinolone use in chickens.

19. Has CVM used any generally accepted statistical methods to correct for the effects of possible confounders in analyzing possible statistical associations between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans? If yes, please specify the confounders considered, the methods used and the difference they made in CVM's risk assessment.

Answer: Yes. CVM used interval estimation which is a generally accepted statistical method. As indicated above, there were two confounders with respect to proportion of fluoroquinolone-resistant *Campylobacter* infections in humans for which a correction was necessary. Uncertainty in the values of the proportions was modeled using a beta distribution which is a standard choice of distribution in the case of proportions. Had the effects of these two confounders not been removed, all the cases of fluoroquinolone-resistant *Campylobacter* infections in humans would have been attributed to the use of fluoroquinolones in chickens.

Two values of attributable fractions (attributed to chicken consumption) were available from case-control studies. Thus, the effects of the other sources or confounders were removed as a block by using the attributable fraction for chicken. Walter (referenced in the risk assessment) showed that an attributable fraction is distributed as log normal. CVM used Monte Carlo simulation to derive a confidence range for the attributable fraction. Monte Carlo draws were made from the lognormal distribution for the two attributable fraction estimates, one from each case-control study. The distribution for the fraction ascribed by the risk assessment model was taken by drawing from a uniform distribution between the two draws from the lognormal distributions. By correcting for these other sources of campylobacteriosis, the estimate for the proportion attributed to chicken consumption was centered at 57%.

20. In analyzing possible statistical associations between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans, did CVM use any generally accepted statistical methods to (a) test for and (b) correct for biases due to the effects of model specification errors and model selection? If yes,

please specify the methods used and the difference they made in CVM's risk assessment.

Answer: (a) No. CVM did not use statistical tests. (b) No. CVM's risk assessment model was epidemiologically-based and fairly straightforward by comparison to other risk assessments. Most of the data used was from large national collections, and there were no comparable replicate data of this type. Hence, there was little means to identify bias due to model specification errors. In terms of selection of distributions for terms in the model, standard choices for each type variable were made. Uniform priors were deemed appropriate since little was known about these variables a priori.

21. In analyzing possible statistical associations between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans, did CVM use any generally accepted statistical methods to (a) test for and (b) correct for biases due to measurement errors in independent variables? If yes, please specify the methods used and the difference they made in CVM's risk assessment.

Answer: (a) No. CVM did not use statistical tests. (b) Yes. CVM did adjust for measurement errors. CVM's risk assessment model was epidemiologically-based and fairly simple by comparison to other risk assessments. Because most of the data used were from large national collections, sampling bias was assumed to be the smallest that it could be. Under the circumstances, the effect of measurement error was accounted for by the use of the uncertainty distributions about the parameter estimates.

22. What does CVM mean by "significant" in its Narrative Statement (p. 3-4) position that "fluoroquinolone-resistant *Campylobacter* species are transferred to humans and are a significant cause of the development of fluoroquinolone-resistant *Campylobacter* infections in humans."

Answer: CVM is using the dictionary definition of the term "significant," i.e., "having or likely to have influence or effect: important"; "probably caused by something other than mere chance."

23. Does CVM have any facts or data demonstrating any increase or decrease in overall *Campylobacter* loads in chickens (and separately for turkeys) since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

Answer:

By "*Campylobacter* loads" we assume that the question refers to the absolute number of *Campylobacter* organisms present on the chickens or turkeys. We interpret "chickens" and "turkeys" to mean live birds.

Chickens

No.

Turkeys
No.

24. Does CVM have any facts or data demonstrating any increase or decrease in overall *Campylobacter* loads in chickens (and separately for turkeys) at the point of sale since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts, or data, please identify.

Answer:

By "*Campylobacter* loads" we assume that the question refers to the absolute number of *Campylobacter* organisms present on the chickens or turkeys. We interpret "chickens" and "turkeys" to mean live birds.

Chickens
No.

Turkeys
No.

25. Does CVM have any facts or data demonstrating any increase or decrease in fluoroquinolone-resistant *Campylobacter* loads in chickens (and separately for turkeys) since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

Answer:

By "*Campylobacter* loads" we assume that the question refers to the absolute number of *Campylobacter* organisms present on the chickens or turkeys. We interpret "chickens" and "turkeys" to mean live birds.

Chickens
No.

Turkeys
No.

26. Does CVM have any facts or data demonstrating any increase or decrease in fluoroquinolone-resistant *Campylobacter* loads in chickens (and separately for turkeys) at the point of sale since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

Answer:

By "*Campylobacter* loads" we assume that the question refers to the absolute number of *Campylobacter* organisms present on the chickens or turkeys. We interpret "chickens" and "turkeys" to mean live birds.

Chickens
No.

Turkeys
No.

27. Does CVM have any facts or data demonstrating any increase or decrease in fluoroquinolone-resistant *Campylobacter* loads in chickens (and separately for turkeys) at the point of consumption since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

Answer:

By "*Campylobacter* loads" we assume that the question refers to the absolute number of *Campylobacter* organisms present on the chickens or turkeys. We interpret "chickens" and "turkeys" to mean cooked meat.

Chickens
No.

Turkeys
No.

28. Does CVM have any facts or data demonstrating any increase or decrease in incidence of campylobacteriosis in humans caused by *C. jejuni* (and separately for *C. coli*) since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

Answer: Yes. Data from FoodNet and from the USDA's Economic Research Service indicates an overall decrease in campylobacteriosis cases during 1996 through 1999. The source of these data and many other studies are available in Docket No. 00N-1571.

29. Does CVM have any facts or data demonstrating any increase or decrease in incidence of fluoroquinolone-resistant campylobacteriosis in humans caused by *C. jejuni* (and separately for *C. coli*) since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

Answer: Yes. CVM has FoodNet data on the incidence of campylobacteriosis and NARMS data on the proportion of *Campylobacter* cases that are fluoroquinolone-resistant. This data can be used to calculate the incidence of fluoroquinolone-resistant campylobacteriosis.

30. Does CVM have any facts or data demonstrating any increase or decrease in incidence rates of fluoroquinolone-resistant campylobacteriosis in humans caused by fluoroquinolone use in chickens and turkeys? If CVM does have such facts or data, please identify.

Answer: Yes, CVM has FoodNet and NARMS data which can be used to calculate such incidence rates. CVM has epidemiological data and information to support an association between fluoroquinolone use in poultry and a change in incidence of fluoroquinolone-resistant campylobacteriosis in humans. These and other data can be found in Docket No. 00N-1571.

31. Does CVM have any facts or data that allow quantitation of the change in incidence rates of fluoroquinolone-resistant campylobacteriosis in humans caused by fluoroquinolone use in chickens and turkeys? If CVM does have such facts or data, please identify.

Answer: No. Fluoroquinolone use data in chickens and turkeys has not been made available to CVM and thus calculations requiring the specific use data cannot be performed. However, NARMS data show an increase in the proportion of fluoroquinolone-resistant campylobacteriosis in humans.

32. Has CVM conducted, or is CVM aware of any, additional analysis of the raw data from the K. E. Smith studies "Fluoroquinolone-Resistant *Campylobacter* Isolated From Humans and Poultry in Minnesota" (G-588) and/or "Quinolone-Resistant *Campylobacter jejuni* Infections in Minnesota, 1992-1998" (G-589) other than as published by the author in those studies; and, if so, what was the conclusion?

Answer: No.

33. Has CVM conducted, or is CVM aware of any, additional analysis of the raw data from H. Kassenborg's studies "Eating Chicken or Turkey Outside the Home Associated With Domestically Acquired Fluoroquinolone-Resistant *Campylobacter* Infections: A FoodNet Case-Control Study" (G-336) and/or "Domestically Acquired Fluoroquinolone-Resistant *Campylobacter* Infections Associated With Eating Poultry Outside the Home" (G-337) other than as published by the author in those studies; and if so, what was the conclusion?

Answer: No.

34. Has CVM conducted, or is CVM aware of any, additional analysis of the raw data from C. Friedman's studies "Risk Factors For Sporadic *Campylobacter* Infections in the United States: A Case-Control Study on FoodNet Sites" (G-228) and/or "Fluoroquinolone-Resistant *Campylobacter* Infections in the United States: A

Pilot Case-Control Study in FoodNet Sites" (G-229) other than as published by the author in those studies; and if so, what was the conclusion?

Answer: Yes. CVM conducted additional analysis of the raw data from some of the variables in the 1998-1999 *Campylobacter* case-control study in FoodNet sites. Specifically, CVM estimated the percentage of cases with a history of travel outside the U.S. and those with a history of fluoroquinolone use prior to culture, categorizing by susceptibility status. CVM estimated that the percentage of cases with a history of foreign travel or prior fluoroquinolone use was 58.1% for those with resistant *Campylobacter* isolates and 26.1% for those with susceptible isolates. More information can be found in CVM's *Campylobacter* risk assessment.

35. Has CVM conducted, or is CVM aware of any, additional analysis of the raw data from N. Marano's study "Fluoroquinolone-Resistant *Campylobacter* Causes Longer Duration of Diarrhea Than Fluoroquinolone-Susceptible *Campylobacter* Strains in FoodNet Sites" (G-394) other than as published by the author in that study; and, if so, what was the conclusion?

Answer: Yes. CVM conducted additional analysis of the raw data from the 1998-1999 *Campylobacter* case-control study in FoodNet sites as described in the answer to No. 34. Also, J. McClellan has conducted additional analysis of this data. The conclusion of this analysis is stated in the presentation described in No. 36 below.

36. Has CVM conducted, or is CVM aware of any, additional analysis of the raw data from J. McClellan presentation "Prevalence and Consequences of Fluoroquinolone-Resistant *Campylobacter* Infections: NARMS 1997 - 2000" other than as presented by the author in the presentation; and, if so, what was the conclusion?

Answer: To the extent that the cited presentation is based upon the raw data from the 1998-1999 *Campylobacter* case-control study in FoodNet sites, yes. CVM conducted additional analysis of the raw data from the 1998-1999 *Campylobacter* case-control study in FoodNet sites as described in the answer to number 34. Also, additional analysis of the data presented by J. McClellan was done by N. Marano.

37. Identify when CVM first understood the existence of a temporal relationship between the use of fluoroquinolones in poultry (including separately chickens and turkeys) and an increase in resistance in *Campylobacter* (including separately *C. jejuni* and *C. coli*) isolates from humans.

Answer: The following answer applies to *C. jejuni* and *C. coli.*

To our best information and belief, CVM first understood that there existed a temporal relationship between the use of fluoroquinolones in chickens and an increase in fluoroquinolone-resistant *Campylobacter* isolates from humans some time

prior to the May 11, 1994 joint meeting of the Veterinary Medicine Advisory Committee and Anti-infective Drugs Advisory Committee (Gaithersburg, Maryland). Although individual CVM employees or other persons now working on CVM's behalf in this matter (e.g., Endtz) may have known earlier of the existence of a temporal relationship between the use of fluoroquinolones in chickens and an increase in fluoroquinolone-resistant *Campylobacter* isolates from humans, it was accepted by CVM management in late 1993 or early 1994.

Because CVM understands that there is no reason for this resistance phenomenon to be different in turkeys than in chickens, CVM's understanding for turkeys developed at the same time as it developed for chickens.

38. If CVM's answer to Interrogatory No. 37 is earlier than October 4, 1996, identify in what way, if any, CVM's <u>current</u> understanding of the temporal relationship between the use of fluoroquinolones in poultry and an increase in resistance in *Campylobacter* isolates from humans <u>differs</u> <u>from</u> CVM's understanding of the issue prior to October 4, 1996.

<u>Answer</u>: CVM's current understanding of the temporal relationship between the use of fluoroquinolones in poultry and an increase in fluoroquinolone-resistant *Campylobacter* isolates from humans differs from CVM's understanding of the issue prior to October 4, 1996 in that <u>currently</u> CVM understands that even with the implementation of strategies intended to prevent or mitigate the development of resistance (approval restrictions, surveillance, and educational activities) due to fluoroquinolone use in poultry, the use of fluoroquinolones in poultry is a significant cause of fluoroquinolone-resistant *Campylobacter* on poultry carcasses and therefore is a significant source of fluoroquinolone-resistant *Campylobacter* infections in humans.

39. In interpreting historical trends and data on associations between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans, did CVM control for internal and external threats to validity of causal inference (specifically including history) (Campbell and Stanley, 1963)? If yes, please specify the control procedures used and/or corrections made in the analysis, and their impacts on CVM's risk assessment.

Answer: Yes. In the CVM risk assessment, demographic characteristics of the population of the FoodNet sites were compared to those of the total U.S. population and were found to be very similar. This similarity supports the validity for applying the FoodNet results to the U.S. general population. Limitations of using data on care-seeking behavior from patients with diarrheal disease in general as a surrogate for care-seeking behavior for persons with campylobacteriosis were explicitly recognized. Controls were age-matched to cases. There were no biases in selection of participants who reported a history of travel outside the country within the past 7 days or having received a fluoroquinolone prior to submitting a stool specimen.

40. Has CVM applied any generally accepted methods of causal inference for interrupted time series and/or quasi-experimental designs to demonstrate a probable causal relation between fluoroquinolone use in chickens and fluoroquinolone-resistant Campylobacter infections in humans? If yes, please specify the data used, analyses performed, and results of these analyses.

Answer: No. Please see responses to Nos. 13-21.

41. In interpreting historical trends and data on associations between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans, did CVM control for the possibility of spurious regression? If yes, please specify the control procedures used and/or corrections made in the analysis, and their impacts on CVM's risk assessment.

Answer: No. Control for spurious regressions and other threats to validity is only necessary when inference is being made from samples not representative of the population to which the inference is being made.

42. Does CVM acknowledge a *lack of* association between poultry use of fluoroquinolones and levels of resistance in *Campylobacter* isolates from humans in certain countries such as Canada, Sweden, Switzerland, Denmark and Turkey? If not, does CVM have an explanation of the poultry and human resistance data from these countries?

Answer: No. CVM cannot acknowledge such a lack of association because there is no indication of what data is being referred to from these countries. CVM acknowledges that data exists from certain countries that has been interpreted by Bayer to demonstrate a lack of association between use of fluoroquinolones in poultry and prevalence of resistance in *Campylobacter* isolates from humans in the countries cited. However, CVM does not acknowledge that these data demonstrate the lack of association because many of the studies do not provide enough information to adequately interpret the data.

43. Does CVM acknowledge the existence of measurable levels of fluoroquinolone resistant *Campylobacter* in humans prior to 1995 as demonstrated in Kiehlbauch (B-

39); Smith (B-59) and Williams (B-67)? If not, does CVM have an explanation of the pre-1995 data in those references?

Answer: Yes. CVM does acknowledge the existence of a low prevalence of fluoroquinolone-resistant *Campylobacter* infections in humans in a community setting prior to 1995. However, the Kiehlbauch and Williams references describe cases that are not representative of those in the general community.

44. Does CVM acknowledge the existence of fluoroquinolone resistance in bacteria other than *Campylobacter* in humans after the introduction of fluoroquinolones in human medicine but prior to 1995, e.g., as documented in Hooper D.C., Wolfson, J.S., "Bacterial Resistance to the Quinolone Antimicrobial Agents"; *Am J Med* 1989 Dec 29;87(6C):17S-23S? Does CVM have an explanation of the pre-1995 data in those references?

Answer: Yes. CVM acknowledges the existence of a very low prevalence of community-acquired fluoroquinolone resistance in bacteria other than *Campylobacter* in humans after the introduction of fluoroquinolones in human medicine but prior to 1995. The pre-1995 data indicates that fluoroquinolone use in humans selects for fluoroquinolone-resistant bacteria.

45. Does CVM acknowledge that "The emergence of resistance to fluoroquinolones in virtually all species of bacteria was recognized soon after the introduction of these compounds for clinical use" (Acar J.F., Goldstein, F.W., "Trends in Bacterial Resistance to Fluoroquinolones"; *Clin Infect Dis* 1997 Jan; 24 Suppl 1:S67-73)? Does CVM have an explanation of the international data on fluoroquinolone resistance emerging in bacteria in humans after clinical use started but before use in animals began?

Answer: Yes. The explanation of the international data is that the use of fluoroquinolones in human medicine can select for fluoroquinolone-resistant bacteria.

46. Does CVM acknowledge that the CVM risk assessment "Human Health Impact of Fluroquinolone-Resistant *Campylobacter* Attributed to the Consumption of Chicken" (October 18, 2000) (G-111) does not follow National Academy of Sciences guidelines for risk assessments? If so, please explain if the Risk Assessment follows any other risk assessment guidelines or principles and identify them. If not, please explain why.

Answer: No. The FDA/CVM model is an antimicrobial resistance risk assessment that follows the National Academy of Sciences (NAS) paradigm as described in Risk Assessment in the Federal Government (1983) and in Science and Judgement in Risk Assessment (1994). Both of these documents were products of the National Research Council (NRC). In addition, the same basic tenets of risk assessment were affirmed by the Institute of Medicine's (IOM) Food Forum at a workshop on Food Safety Policy, Science, and Risk Assessment:

Strengthening the Connection (1999). The consensus is that the elements of a comprehensive risk assessment are (1) hazard identification, (2) exposure assessment, (3) hazard characterization, and (4) quantitative health risk assessment. It should be noted that one component of hazard characterization is a dose response assessment and in some citations the term dose response assessment is in place of hazard characterization.
The FDA/CVM antimicrobial resistance risk assessment followed the NAS paradigm as indicated. The FDA/CVM risk assessment:

(1) identifies the hazard as fluoroquinolone resistance in *Campylobacter* attributed to use of fluoroquinolones in chickens among persons who seek care for campylobacteriosis and are prescribed a fluoroquinolone,

(2) assesses exposure of humans to fluoroquinolone-resistant *Campylobacter* by quantifying the amount of chicken consumed per year, the proportion of chicken that carry *Campylobacter* and the prevalence of resistance among the chicken with *Campylobacter* tested for fluoroquinolone sensitivity,

(3) characterizes the hazard by relating the quantity of chicken contaminated with fluoroquinolone-resistant *Campylobacter* to the number of persons who seek care for campylobacteriosis which is attributed to chicken and whose *Campylobacter* isolates are resistant to fluoroquinolones, and

(4) quantifies the health risk as the probability of experiencing the hazardous outcome.

CVM's risk assessment model quantifies the incremental impact of fluoroquinolone resistance among human campylobacteriosis cases attributable to the use of fluoroquinolones in chickens.

47. Does CVM acknowledge that the CVM risk assessment "Human Health Impact of Fluroquinolone-Resistant *Campylobacter* Attributed to the Consumption of Chicken" (October 18, 2000) does not follow National Academy of Sciences guidelines for hazard identification, specifically by failing to identify or specify adverse human health effects that have been shown to be causally associated with exposures to *Campylobacter*?

Answer: No. CVM appropriately identified the adverse human health effects of fluoroquinolone-resistant *Campylobacter* attributed to the consumption of chicken.

48. Does CVM acknowledge that the CVM risk assessment "Human Health Impact of Fluroquinolone-Resistant *Campylobacter* Attributed to the Consumption of Chicken" (October 18, 2000) does not follow National Academy of Sciences guidelines for exposure assessment, specifically by failing to quantify or characterize

probable levels (or frequency distributions) of individual exposures to *Campylobacter*?

Answer: No. Again, CVM finds that the question mis-specifies the focus of the exposure assessment as having to do with *Camplobacter*, per se. CVM also disagrees that we failed to characterize probable levels (frequency distributions) of exposures to fluoroquinolone-resistant *Campylobacter* from chicken. The probability distribution for the quantity of chicken contaminated with fluoroquinolone-resistant *Campylobacter* is provided. It represents the probability distribution for the exposure at the population level. Division by the number of people who consume chicken yields the exposure distribution for an average consumer. The exposure is adjusted higher for persons who consume more and lower for those who consume less than average.

49. Does CVM acknowledge that the CVM risk assessment "Human Health Impact of Fluroquinolone-Resistant *Campylobacter* Attributed to the Consumption of Chicken" (October 18, 2000) does not follow National Academy of Sciences guidelines for risk assessment, specifically by failing to quantify or characterize an exposure-response relation for *Campylobacter* and campylobacteriosis?

Answer: No. CVM established, through the parameter K_{res}, an exposure-response relationship between the quantity of chicken contaminated with fluoroquinolone-resistant *Campylobacter* and the number of human cases with fluoroquinolone-resistant *Campylobacter*.

50. Does CVM acknowledge that the CVM risk assessment "Human Health Impact of Fluroquinolone-Resistant *Campylobacter* Attributed to the Consumption of Chicken" (October 18, 2000) does not follow National Academy of Sciences guidelines for uncertainty characterization in its risk assessment?

Answer: No. CVM ascribed uncertainty based on sampling variation to estimated parameters in our model. Model uncertainty was not described because the model consisted of only 4 main modules:

1. Developing uncertainty distributions for the CDC FoodNet estimate of all campylobacteriosis cases,
2. Estimating the number of all human cases that were resistant and attributed to the use of fluoroquinones in chickens that would be receiving a fluoroquinolone and its uncertainty distribution,
3. Developing uncertainty distributions for the amount of chicken contaminated with fluoroquinolone-resistant *Campylobacter*, and
4. Estimating the parameter describing the exposure-response relationship between 2 and 3 and its uncertainty distribution.

51. Identify all facts and data on which CVM relies for its position that fluoroquinolone-resistant *Campylobacter* infections (caused by *C. jejuni,* and separately, *C. coli*) have the potential to adversely affect human health.

Answer: Facts and data on which CVM relies for its position that fluoroquinolone-resistant *Campylobacter* infections have the potential to adversely affect human health can be found in Docket No. 00N-1571 (to include CVM's Notice of Opportunity for Hearing and *Campylobacter* Risk Assessment).

52. Identify when CVM first understood that fluoroquinolone-resistant *Campylobacter* infections (caused by *C. jejuni,* and separately, *C. coli*) have the potential to adversely affect human health.

Answer: For *Campylobacter jejuni* and *Campylobacter coli*:

To our best information and belief, CVM first understood that fluoroquinolone-resistant *Campylobacter* infections have the potential to adversely affect human health some time prior to the May 11, 1994 joint meeting of the Veterinary Medicine Advisory Committee and Anti-infective Drugs Advisory Committee (Gaithersburg, Maryland). Although individual CVM employees or other persons working on CVM's behalf in this matter may have known that fluoroquinolone-resistant *Campylobacter jejuni* and coli have the potential to adversely effect human health earlier, it was accepted by CVM management in late 1993 or early 1994.

53. If CVM's answer to Interrogatory No. 52 is earlier than October 4, 1996, identify in what way, if any, CVM's current understanding that fluoroquinolone-resistant *Campylobacter* infections (caused by *C. jejuni,* and separately, *C. coli*) have the potential to adversely effect human health differs from its understanding of the potential prior to October 4, 1996.

Answer: CVM's current understanding that fluoroquinolone-resistant *Campylobacter* infections have the potential to adversely affect human health differs from its understanding of the potential prior to October 4, 1996 in that we now know that even with the implementation of strategies intended to prevent or mitigate the development of resistance (approval restrictions, surveillance, and educational activities) due to fluoroquinolone use in poultry, the use of fluoroquinolones in poultry is a significant cause of fluoroquinolone-resistant *Campylobacter* on poultry carcasses and a significant source of fluoroquinolone-resistant *Campylobacter* infections in humans. Further, the CVM *Campylobacter* risk assessment and new surveillance data gives a better understanding of the potential for fluoroquinolone-resistant *Campylobacter* to adversely affect human health.

54. Does CVM contend that infections caused by fluoroquinolone-resistant *Campylobacter* (caused by *C. jejuni,* and separately, *C. coli*) have a greater adverse

affect on human health than infections caused by fluoroquinolone-susceptible *Campylobacter?*

Answer: Yes. Individuals infected with fluoroquinolone-resistant organisms are more likely to suffer greater adverse effects than those infected with fluoroquinolone-susceptible organisms.

55. If CVM's answer to Interrogatory No. 54 is anything other than an unqualified "no," please identify all facts and data upon which CVM relies to supports its contention.

Answer: Studies have shown that fluoroquinolone resistance in *Campylobacter* leads to increased duration of diarrheal illness and increased rates of hospitalization. A discussion of additional facts and information to support this response may be found in Docket No. 00N-1571.

56. Does CVM have any facts or data demonstrating any increase in severity of infections caused by fluoroquinolone-resistant *Campylobacter* (*C. jejuni*, and separately, *C. coli*) as compared to infections caused by fluoroquinolone-susceptible (non-resistant) *Campylobacter* (*C. jejuni*, and separately, *C. coli*)? If CVM does have such facts or data, please identify the increase in severity, identify all facts and data on which CVM relies, and identify when CVM first learned of such facts or data.

Answer: Yes. CVM does have data demonstrating an increase in severity of infections caused by fluoroquinolone-resistant *Campylobacter*. A FoodNet *Campylobacter* case-control study (Friedman *et al.*) showed that patients with ciprofloxacin-resistant *Campylobacter* infections had higher hospitalization rates than patients with ciprofloxacin-susceptible infections. Furthermore, several studies showed that patients with fluoroquinolone-resistant *Campylobacter* infections have a longer duration of illness than those with susceptible infections (FoodNet *Campylobacter* case-control study, Smith *et al.*, and Neimann *et al.*). The FoodNet *Campylobacter* case-control study and the Neimann study do not distinguish between *Campylobacter* species. The Smith study describes patients infected with *C. jejuni*. These references and other supportive documents are in Docket No. 00N-1571. We are not aware of any studies that describe severity of illness for *C. coli* separately. CVM became aware of these studies as they became available.

57. Does CVM have any facts or data demonstrating any increase in duration of illness from infections caused by fluoroquinolone-resistant *Campylobacter* (*C. jejuni*, and separately, *C. coli*) as compared to infections caused by fluoroquinolone-susceptible (non-resistant) *Campylobacter* (*C. jejuni*, and separately, *C. coli*)? If CVM does have such facts or data, please identify the increase in duration of illness, identify all facts and data on which CVM relies, and identify when CVM first learned of such facts or data.

Answer: Yes. The data of which CVM is aware are contained in answer 56 above. In addition, the FoodNet *Campylobacter* case-control study showed that the association between ciprofloxacin-resistant *Campylobacter* isolates and longer mean duration of diarrhea occurred both among patients who took ciprofloxacin for their illness and among those who did not. These references and other supportive documents are in Docket No. 00N-1571. We are not aware of any studies that describe duration of illness for *C. coli* separately. CVM became aware of these studies as they became available.

58. Does CVM have any facts or data demonstrating any other adverse human health consequences from infections caused by fluoroquinolone-resistant *Campylobacter* (*C. jejuni* and separately, *C. coli*) as compared to infections caused by fluoroquinolone-susceptible (non-resistant) *Campylobacter* (*C. jejuni* and separately, *C. coli*)? If CVM does have such facts or data, please identify the other adverse consequences, identify the facts and data on which CVM relies and identify when CVM first learned of such facts or data.

Answer: Yes. An "agent" of CVM (for purposes of this hearing) has informed CVM of the existence of an additional study in which preliminary analysis demonstrates increased mortality associated with fluoroquinolone-resistant *Campylobacter* infections compared to fluoroquinolone-susceptible *Campylobacter* infections. However, CVM has not yet reviewed this study. CVM learned of this study while preparing its responses to these Interrogatories.

59. Identify all complications CVM is aware of that are associated with infections caused by fluoroquinolone-resistant *Campylobacter* that are not associated with infections caused by fluoroquinolone-susceptible (non-resistant) *Campylobacter*? If CVM is aware of any such complications, please identify all facts or data in support and identify when CVM first learned of such facts or data.

Answer: Yes. Patients don't respond to fluroquinolone therapy. An "agent" of CVM (for purposes of this hearing) has informed CVM of the existence of an additional study in which additional analysis demonstrates increased mortality associated with fluoroquinolone-resistant *Campylobacter* infections compared to fluoroquinolone-susceptible *Campylobacter* infections. However, CVM has not yet reviewed this study. CVM learned of this study while preparing its responses to these Interrogatories.

60. Does CVM have any facts or data demonstrating any increase in the rate or extent of complications (including but not limited to Guillian-Barre syndrome) from infections caused by fluoroquinolone-resistant *Campylobacter* as compared to infections caused by fluoroquinolone-susceptible (non-resistant) *Campylobacter*? If CVM does have such facts or data, please identify the increase in the rate or extent of complications, identify the facts and data on which CVM relies and identify when CVM first learned of such facts or data.

Answer: No. However, the absence of such data does not preclude that these adverse outcomes may occur at increased rates in patients infected with fluoroquinolone-resistant *Campylobacter*.

61. CVM's Notice of Opportunity for Hearing states "The current level of resistance among human *Campylobacter* isolates attributed to the use of fluoroquinolones in poultry represents a harm to human health." 65 FR 64955. Does CVM accept some level of resistance among human *Campylobacter* isolates attributed to the use of fluoroquinolones in poultry greater than zero that would *not* constitute a harm to human health. If so, what is that level?

Answer: No.

62. CVM's Narrative Statement (p. 5) states "The magnitude of the benefit of antibiotic treatment is directly related to the early initiation of therapy." Identify specifically, by number of days after symptoms commence, what CVM means by "early initiation of therapy". Identify at what point CVM believes therapy is no longer effective.

Answer: The precise definition of "early" varies depending on the reference. We are not aware of a standard definition for "early." We are also not aware of a consistently demonstrated specific point where therapy is no longer effective.

63. How does CVM define *in vitro Campylobacter* resistance (i.e. at what minimum inhibitory concentration) for *C. jejuni* (and separately for *C. coli*)? To the extent that CVM defines resistance as an MIC of >4 µg/ml, identify all facts or data CVM relies on to support that infection with *Campylobacter* having an *in vitro* MIC of >4 µg/ml would result in an adverse impact on treatment if the patient was prescribed a fluoroquinolone.

Answer: We view the use of greater than or equal to 4 µg/mL as a scientifically valid ciprofloxacin resistance breakpoint for both *C. jejuni* and *C. coli* (and favorable to Bayer for the purposes of this hearing). *Campylobacter* typically display a biomodal distribution of susceptibility phenotypes. Among those reported by the NARMS for 2000, the modes for ciprofloxacin were below 0.19 µg/mL and greater than or equal to 24 µg/mL, with very few intermediate phenotypes.

There is no NCCLS recognized ciprofloxacin resistant breakpoint for *Campylobacter*. However, a similar professional organization in the United Kingdom, the British Society for Antimicrobial Chemotherapy (BSAC), has a working group on susceptibility testing and published a tentative ciprofloxacin resistant breakpoint of ≥4 µg/mL for *Campylobacter spp.* (King 2001). Additionally, CVM is aware that the Denmark surveillance system (DANMAP) uses a ciprofloxacin breakpoint of >2 µg/mL.

Regarding the negative impact to patient health with organisms displaying ciprofloxacin MICs ≥4 μg/mL, evidence in Docket No. 00N-1571 shows that patients infected with these strains have prolonged illness.

Evidence in Docket No. 00N-1571 shows that patients infected with these strains have prolonged illness, increased hospitalization and other possible severe consequences.

64. Is CVM aware of any analysis of NARMS *Campylobacter* resistance data examining year-to-year patterns of change of susceptibility of isolates over the entire range of MICs tested?

Answer: Yes.

65. Does CVM have knowledge of the portion of fluoroquinolone-resistant Campylobacter infections in humans reported by NARMS that were acquired outside the United States? If so, identify the portion for the years 1997, 1998, 1999, and 2000.

Answer: Yes. A portion of the fluoroquinolone-resistant *Campylobacter* infections in humans reported by NARMS that are acquired outside the United States may be estimated based on information gathered in the H. Kassenborg study "Eating Chicken or Turkey Outside the Home Associated With Domestically Acquired Fluoroquinolone-Resistant *Campylobacter* Infections: A FoodNet Case-Control Study" and/or "Domestically Acquired Fluoroquinolone-Resistant *Campylobacter* Infections Associated With Eating Poultry Outside the Home" (Exhibits G-336 and G-337).

66. Does CVM have knowledge of the portion of fluoroquinolone-resistant *Campylobacter* infections in humans reported by NARMS that were acquired inside the United States? If so, identify the portion for the years 1997, 1998, 1999, and 2000.

Answer: Yes. See answer to No. 65 above.

67. Does CVM have knowledge of the portion of fluoroquinolone-resistant *Campylobacter* infections in humans reported by NARMS that were acquired inside the United States, where the patient had a history of prior fluoroquinolone use within the previous 30 days? If so, identify the portion for the years 1997, 1998, 1999, and 2000.

Answer: Yes. See answer to No. 65 above.

68. Other than as specifically referenced in the Notice of Opportunity for Hearing, Notice of Hearing and Risk Assessment, identify any additional basis for CVM's assertion that severe enteric diseases are treated empirically.

Answer: The documentary information requested can be found in Docket No. 00N-1571. CVM is also aware that standard clinical practice includes empiric treatment of severe enteric diseases.

69. Identify any populations in the United States of which CVM is aware for which severe enteric disease are and are *not* treated empirically.

Answer: CVM does not have data specifically related to usage of antibiotics in enteric disease based on severity. Treatment recommendations for diarrheal illness recommend that patients with severe disease receive antimicrobial treatment. Since the time it takes to isolate a pathogen may be several days, treatment is usually initiated empirically. CVM is not aware of any guidelines that suggest withholding therapy in any populations of patients with severe enteric disease.

70. In light of the antibiotic resistance issues, the risk of the hemolytic-uremic syndrome (HUS) after antibiotic treatment of severe enteric infections caused by *Escherichia coli* 0157:H7, and other issues, does CVM believe there is a trend toward less empiric treatment of severe enteric disease?

Answer: No.

71. Identify all facts and data, of which CVM is aware, if any, to demonstrate that *Campylobacter coli* is a human pathogen or a human health hazard.

Answer: Although it is less common than *Campylobacter jejuni*, *Campylobacter coli* has been described as a cause of human illness. In clinical practice, some laboratories may not speciate *Campylobacter* organisms, so the true incidence of disease with *C. coli* may be higher than estimated. Supporting facts and data may be found in Docket No. 00N-1571.

72. Identify all facts and data on which CVM relies to demonstrate that there is a reasonable basis from which serious questions may be inferred about the safety of Enrofloxacin for the control of mortality in turkeys associated with *E. coli* and *Pasteurella multocida* organisms. If none, please state CVM's basis for the belief.

Answer: FDA is proposing to withdraw approval of the NADA for use of enrofloxacin in poultry (which includes turkeys) based on CVM's determinations that the use of fluoroquinolones in poultry (including turkeys) causes the development of fluoroquinolone-resistant *Campylobacter* in poultry; this resistant Campylobacter is transferred to humans and is a significant cause of resistant *Campylobacter* infections in humans; and resistant *Campylobacter* infections are a human health hazard. The proposal to withdraw the NADA is on the grounds that new evidence shows that the product has not been shown to be safe as provided for in the Federal Food, Drug, and Cosmetic Act (the act).

While CVM recognizes that turkeys and chickens are separate species, the limited data that is available on fluoroquinolone susceptible and resistant *Campylobacter* isolated from turkeys and turkey products indicate epidemiological similarities between the two species with regard to transfer of these organisms to humans. The routes of infection of turkeys and the methods of carcass contamination leading to the presence of *Campylobacter* on turkey food products are similar to those responsible for infection of chickens and contamination of chicken meat.

The facts and data to support this response may be found in Docket No. 00N-1571.

73. Identify all data in CVM's possession showing levels of fluoroquinolone-resistant *Campylobacter spp.* in turkeys.

Answer: The information requested in this interrogatory can be found in Docket No. 00N-1571.

74. Identify all epidemiological studies that CVM contends demonstrate a strong association between eating chickens (and separately for turkeys) and acquiring human *Campylobacter* infections as well as all epidemiological studies demonstrating a strong association between eating chickens (and separately for turkeys) and acquiring fluoroquinolone-resistant *Campylobacter* infections.

Answer: Numerous studies, including those noted in the Notice of Opportunity for Hearing, have indicated a strong association between eating chickens (and therefore, by extrapolation to turkeys) and acquiring both human fluoroquinolone-susceptible and fluoroquinolone-resistant *Campylobacter* infections. The CVM risk assessment established an estimate for the human health impact due to use of fluoroquinolones in chickens. A study conducted in Minnesota (Smith *et al.*) found that since the approval of fluoroquinolones for use in poultry, the percentage of confirmed *C. jejuni* infections that were resistant to quinolones and acquired domestically more than tripled, from 1996 to 1998. A CDC FoodNet case-control study of patients with fluoroquinolone-resistant *Campylobacter* infections and well controls (Kassenborg *et al.*) determined that illness was associated with eating chicken or turkey in commercial establishments. These studies and other supportive information may be found in Docket No. 00N-1571.

75. Does CVM acknowledge that multiple epidemiological studies demonstrate a significant negative association between handling, cooking, and eating chickens at home and acquiring human *Campylobacter* infections?

Answer: No. CVM has reviewed the conclusions of only one study, by C. Friedman (exhibit G-228) where the author concluded "eating chicken or turkey cooked at home was a protective factor" for the acquisition of campylobacteriosis. However, an "agent" of CVM (for purposes of this hearing) has informed CVM of the existence of additional studies. CVM itself has not yet reviewed these additional studies.

76. Identify all studies CVM believes link the genetic make-up of *Campylobacter* isolates from chickens (and separately for turkeys) and humans.

Answer: To our best belief and knowledge, the information requested in this interrogatory can be found in Docket No. 00N-1571.

77. Explain why CVM believes that it is biologically implausible that the level of fluoroquinolone-resistant human *Campylobacter* infections in the United States is due to fluoroquinolone use in humans or the spread of resistant *Campylobacter* infections from one human to another.

Answer: CVM believes that it is biologically plausible that a portion of the fluoroquinolone-resistant human *Campylobacter* infections in the United States is due to fluoroquinolone use in humans. CVM also believes that it is biologically plausible that a portion of the fluoroquinolone-resistant human *Campylobacter* infections in the United States is due to the spread of resistant *Campylobacter* infections from one human to another. However, the relative contribution of fluoroquinolone-resistant human *Campylobacter* infections from these two sources in comparison to cases acquired due to the consumption of undercooked poultry or foods cross-contaminated by poultry is very small. Furthermore, although person-to-person transmission of some bacteria is common, person-to-person transmission of *Campylobacter* occurs infrequently. Supporting information can be found in Docket No. 00N-1571.

78. Does CVM acknowledge that human *Campylobacter* infections in the United States have sometimes been caused by the spread of *Campylobacter* infections from one human to another?

Answer: Yes. However, CVM believes that the incidence of person-to-person transmission of *Campylobacter* in the U.S. is low.

79. Does CVM believe that fluoroquinolone resistant *Campylobacter* infections in humans existed in the United States prior to 1995?

Answer: Yes. The use of fluoroquinolones to treat *Campylobacter* infections in humans can lead to the selection of resistance during therapy. In addition, people may have acquired fluoroquinolone-resistant *Campylobacter* infections while traveling abroad.

80. If CVM's response to Interrogatory No. 79 is "no," identify all facts and data supporting CVM's belief.

Answer: Not applicable.

81. Does CVM believe that fluoroquinolone-resistant *Campylobacter* (*C. jejuni*, and separately, *C. coli*) bacteria existed in chickens (and separately for turkeys) in the United States prior to 1995?

Answer: Yes. The existence of *Campylobacter* mutants resistant to fluoroquinolones, albeit low in prevalence, is a natural phenomenon that can be expected to occur once in approximately 5 x 10^8 cells [1 in 50 million] (Gootz 1991), regardless of the host species.

82. If CVM's response to Interrogatory No. 81 is "no," identify all facts and data supporting CVM's belief.

Answer: Not applicable.

83. Identify all human health risks and benefits of enrofloxacin use in chickens (and separately for turkeys) that FDA/CVM considered in making the decision to withdraw the NADA for enrofloxacin. In none, please explain why none were considered.

Answer: FDA/CVM has not yet made a decision on whether to withdraw the NADA for enrofloxacin. That decision will be made at the conclusion of the enrofloxacin hearing based on the record of that hearing. The information CVM considered in making the decision to *propose* to withdraw the NADA for enrofloxacin has already been provided to Bayer in CVM's Notice of Opportunity for a Hearing, 65 Fed. Reg. 64954 (October 31, 2000). Additional documentation can be found in Docket No. 00N-1571.

84. Identify all animal health risks and benefits of enrofloxacin use in chickens (and separately for turkeys) that FDA/CVM considered in making the decision to withdraw the NADA for enrofloxacin. If none, please explain why none were considered.

Answer: See answer to No. 83 above.

85. Identify all environmental risks and benefits of enrofloxacin use in chickens (and separately for turkeys) that FDA/CVM considered in making the decision to withdraw the NADA for enrofloxacin. If none, please explain why none were considered.

Answer: See answer to No. 83 above.

86. Identify all economic risks and benefits of enrofloxacin use in chickens (and separately for turkeys) that FDA/CVM considered in making the decision to withdraw the NADA for enrofloxacin. If none, please explain why none were considered.

Answer: See answer to No. 83 above.

87. If the NADA for enrofloxacin is withdrawn, what drugs, if any, does CVM believe are available for the control of mortality in chickens associated with *E. coli* organisms, and available for the control of mortality in turkeys associated with *E. coli* and *Pasteurella multocida* organisms?

Answer: The following table shows the drugs that are currently approved for the prevention, control, or treatment of *E. coli* infections in chickens and *E. coli* and *P. multocida* infections in turkeys. For each drug, we have provided the drug name, the dosage form, the approved species, and the product indication.

In addition to the drugs listed in this table, under the Animal Medicinal Drug Use Clarification Act of 1994 and the implementing regulations promulgated in 1996, a veterinarian can, under certain circumstances, prescribe the extralabel use of a drug approved in another species or in the same species for another indication. Therefore, if a veterinarian determines that none of the drugs listed in the table is effective for the indications listed, he or she has access to many other antimicrobials.

Drug	Dosage form	Approved species	Product indication
Ceftiofur sodium	injectable	day-old chickens	For control of early mortality associated with *E. coli* susceptible to ceftiofur.
Ceftiofur sodium	injectable	day-old turkeys	For control of early mortality associated with *E. coli* susceptible to ceftiofur.
Chlortetracycline	oral	chickens	Control of infectious synovitis caused by *M. synoviae*; chronic respiratory disease and air-sac infections caused by *M. gallisepticum* and *E. coli*; and mortality due to fowl cholera caused by *P. multocida*. Treatment of chronic respiratory diseases. Reduction of mortality due to *E. coli* infections.
Gentamicin	injectable	day-old chickens	Prevention of early mortality associated with E. coli, S. typhimurium, and P. aeruginosa susceptible to gentamicin.
Oxytetracycline	oral	chickens	Control of infectious synovitis caused by M. synoviae; chronic respiratory disease and air sac infections caused by M. gallisepticum and E. coli; and fowl cholera caused by P. multocida.
Oxytetracycline	oral	turkeys	Control of infectious synovitis caused by M. synoviae; complicating bacterial organisms associated with bluecomb.
Oxytetracycline	injectable	chickens and turkeys	Treatment of air sacculitis and caused by M. gallisepticum and E. coli; fowl cholera caused by P. multocida; infectious sinusitis caused by M. gallisepticum; and infectious synovitis caused by M. synoviae.

Drug	Dosage form	Approved species	Product indication
Spectinomycin dihydrochloride pentahydrate	injectable	1- to 3-day-old turkeys	Prevent mortality associated with Arizona group infection; control chronic respiratory disease associated with E. coli.
Spectinomycin dihydrochloride pentahydrate	injectable	1- to 3-day-old chickens	Control of mortality associated with infections caused by M. synoviae, S. typhimurium, S. infantis, and E. coli.
Sulfomyxin	injectable	1- to 3-day-old chickens	Aid in treatment of disease caused or complicated by E. coli.
Tetracycline	oral	chickens	Control of chronic respiratory disease caused by M. gallisepticum and E. coli; and control of infectious synovitis caused by M. synoviae.

88. With regard to each drug identified in response to Interrogatory No. 87, identify specifically, all studies which assess: the human health impact of each drug when used in chickens or turkeys, the animal health impact of each drug when used in chickens or turkeys, the impact of the drug on chicken and turkey pathogen loads, and the potential for residues on chicken and turkey carcasses.

Answer: CVM objects to this question as being overly burdensome. Not withstanding that objection, CVM provides the following answer: Each of the drugs identified in response to Interrogatory No. 87 has an approved new animal drug application, which includes a publicly available Freedom of Information summary. The Freedom of Information summary outlines the studies that assessed the human food safety of the drug as well as the animal health impact of the drug. Studies done under CFR 558.15 that assessed pathogen load are also described in the Freedom of Information summary. The Freedom of Information summary is published in the Federal Register as part of the notice of the approval. The summaries can also be accessed on the Internet from the CVM Home Page.

The new animal drug approval process requires that every drug approved for use in a food-producing animal have both a slaughter withdrawal period and a tolerance set prior to approval. A description of the studies used to establish the tolerance and the withdrawal period may be found in the Freedom of Information summary for the drug. If the drugs are used according to the labeled indications shown in the table and the slaughter withdrawal period is adhered to, the potential for drug residues is considered as part of safety studies required for drug approval.

89. Identify all pending studies, including protocols and requests for proposals, that are being conducted by CVM or otherwise known by CVM that address the emergence and dissemination of fluoroquinolone-resistant *Campylobacter spp.* in chickens and/or turkeys.

Answer:

(a) FDA Proposal Number: FD-U-001868-01 "Does antibiotic usage create drug-resistant *Campylobacter*"? Margie D. Lee, DVM PhD, Dept. Medical Microbiology and Parasitology The University of Georgia Athens, GA 30602.

(b) USDA 2001-02136 Prevalence, Strain Types and Antibiotic Resistance of *Campylobacter* in Turkey Grow-out Farms. Kathariou, S.; Carver, D. North Carolina State University; Department of Food Science; Raleigh, NC 27695 Grant 2001-35212-10843.

(c) USDA 2001- 02147. Clonal Dissemination of Antimicrobial Resistant *Campylobacter jejuni* and *Escherichia coli.* Besser, T.E.; Sischo, W.M.; Hancock,

D.D. Washington State University, Department of Veterinary Microbiology and Pathology, Pullman WA 99164-7040. Grant 2001-35212-10842.

(d) USDA 9904289 Dynamics of *Campylobacter* Transmission on Poultry Farms. Zhang, Q.; Morishita, T.Y. The Ohio State University; Department of Veterinary Preventive Medicine; Wooster, OH 44691. Grant 99-35212-8517.

(e) USDA 6612-32000-035-00D Antimicrobial Resistance in Pathogenic and Commensal Bacteria of Food Animals. Cray, P.J.; Englen, M.D.; Gray, J.T.; Hudson, C.R.; Agricultural Research Service; Athens, GA.

(f) USDA Factors Affecting the Emergence of Quinolone-Resistant *Campylobacter* in Poultry. Zhang, Q., Ohio State University, Cooperative State Research Education and Extension.

(g) Antibiotic Resistance Integrons in Shiga Toxin-Producing *Escherichia coli & Campylobacter jejuni/coli.* Meng, J.; White, D.; Zhao, S.; Wagner, D.; University of Maryland, FDA/CVM Office of Research; Laurel, MD.

(h) USDA 6202-42000-013-00 Antibiotic Resistance to Enteric Bacteria in Poultry or Food-Producing Animals. Bischoff, K.M.; Beier, R.C.; Genovese, K.J.; Poole, T.L.; Agricultural Research Service Agricultural Research Center, Southern Plains Area; TX.

(i) USDA 6202-42000-001-07S Evaluation of Salmonella and Campylobacter Recovery Incidence in Commercial Turkeys. Byrd, J.A.; Caldwell, D.J.; Texas A&M University; Agricultural Research Service.

(j) USDA 6612-42000-031-00 *Campylobacter* Epidemiology, Methods Development & Interventions in Poultry. Agricultural Research Service, Peanut Research; South Atlantic Area, GA.

(k) USDA 6612-32000-025-00D *Campylobacter* Epidemiology, Methods Development & Interventions in Poultry. Stern, N.J.; Line, J.E.; Siragusa, G.; Cox, N.A.; Hiett, K.L.; Agricultural Research Service; Athens, GA.

(l) USDA 6612-32000-024-00D Antimicrobial Resistance Research. Cray, P.J.; Gray, J.T.; Hudson, C.R.; Englen, M.D. Agricultural Research Service; Athens, GA.

(m) FDA E0705001 Studies on the Fluoroquinolone Resistance in *Campylobacter* spp. Isolated from Poultry, Nawaz M. FDA/NCTR.

90. Identify all pending studies, including protocols and requests for proposals, that are being conducted by CVM or otherwise known by CVM that address the transfer of fluoroquinolone-resistant *Campylobacter* from chickens and/or turkeys to humans.

Answer:

(a) FDA Proposal Number 223-01-7008 "Survey of antibiotic resistant bacteria in food animals, poultry workers and human referent groups". Stine, O.C., Dept. of Pediatrics, University of Maryland; College Park, MD.

(b) USDA 2001-02977 Genetic Characterization of *Campylobacter* Major Outer Membrane Protein. Zhang, Q. The Ohio State University; Food Animal Health Research Program/ OARDC; Wooster, OH 44691. Grant 2002-35201-11669.

(c) USDA 2000-02446 Immunoelectrochemical/Optical Biosensor with a Capillary Bioseparator/Bioreactor for Rapid Detection of Pathogens in Poultry and Meat Products. Li, Y.; Liu, Y. University of Arkansas; Department of Poultry Science; Fayetteville, AR 72701. Grant 01-35201-10056.

(d) USDA 9902873 Molecular Characterization of the *Campylobacter jejuni* Adhesin to Fibronectin. Konkel, M.E. Washington State University; Department of Microbiology; Pullman, WA 99164-4233. Grant 99-35201-8579.

(e) FDA/CVM 402.03 Characterization of Antimicrobial Resistance Among Bacteria Isolated from Retail Meats: Expansion of the NARMS Program. White, DG. FDA/CVM Office of Research, Laurel, MD.

(f) FDA/CVM 406.01 Antibiotic Resistance of Foodborne Bacterial Pathogens Isolated from Retail Meats from the State of Iowa. White, DG. FDA/CVM Office of Research, Laurel, MD.

(g) Maryland Agricultural Experiment Station Antibiotic-Resistant *Campylobacter* Isolated from Retail Meats. Meng, J. University of Maryland, College Park, MD.

(h) USDA 5438-42000-006-00 Of Zoonotic Pathogen Transmission from Animal Manure to Human Food. Laster, D.B., Agricultural Research Service, Meat Animal Research Center. Northern Plains Area.

(i) USDA 6612-41420-007-00 Microbial Ecology and Transmission of Human Pathogens in the Poultry Processing Plant. Meinersmann, R.J.; Berrang, M.E.; Lyon, C.E. Agricultural Research Service; South Atlantic Area, Peanut Research.

(j) USDA 6612-41420-012-00D Reduction and Control of Pathogens Associated with Food Processing Surfaces. Arnold,

(k) USDA 5438-32000-021-00D Prevention of Zoonotic Pathogen Transmission from Animal Manure to Human Food. Berry, E.D. Agricultural Research Service; Clay Center.

(l) USDA 6612-41420-010-00D Microbial Ecology and Transmission of Human Pathogens During Poultry Processing. Meinersmann, R.J.; Berrang, M.E.; Lyon, C.E.; Agricultural Research Service; Athens, GA.

(m) USDA 98-35201-6195 Role of Putative Pathogenicity Island in *Campylobacter jejuni* Virulence (1998-02745). Joens, L.A. University of Arizona.

(n) USDA 5325-32000-002-00D Treatment of Animal Manure to Prevent Pathogen Transmission. Mandrell, R.E.; Ravva, S.V.; Duffy, B.K. Agricultural Research Service; Albany, CA.

(o) USDA 6612-42000-023-01T National Epidemiologic and Intervention...*Salmonella & Campylobacter* to Processed Carcasses. Stern, N.J.; Cray, P.J.; Meinersmann, R.J.; Line, E.; Bailey, J.S.; Cox, N.A.; Craven, S.E.; Kelly, L.C. Agricultural Research Service, Athens, GA.

91. Identify all pending studies including protocols and requests for proposals, that are being conducting by CVM or otherwise known by CVM that address whether fluoroquinolone-resistant *Campylobacter* infections have the potential to adversely effect human health.

Answer: CVM understands that Bayer's witness Louis Anthony Cox, Jr. has done further *Campylobacter* risk assessment work and that there are rumors that there is a "Harvard Risk Assessment" on *Campylobacter*.

I declare under penalty of perjury that the foregoing is true and correct. Executed on July 26, 2002.

Stephen Sundlof, D.V.M., Ph.D.
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Respectfully submitted, with objections, this 26th day of July, 2002, by:

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Enrofloxacin Hearing
Docket No: 00N-1571

CERTIFICATE OF SERVICE

I hereby certify that an original and two copies of the foregoing Center for Veterinary Medicine's Responses to Bayer's June 24, 2002, Interrogatories was hand delivered this 26th day of July, 2002, to:

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane (Room 1061)
Rockville, MD 20852

I also certify that a copy of the Response has been hand delivered and e-mailed, this 26th day of July, 2002, to:

The Office of the Administrative Law Judge (ddavidso@oc.fda.gov)
Food and Drug Administration
Room 9-57, HF-3
5600 Fishers Lane
Rockville, MD 20857

I also certify that a copy of the Response was e-mailed, mailed by first class mail, postage prepaid, and hand delivered, this 26th day of July, 2002, to:

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Dated: 7/26/02

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